REMARKS/ARGUMENTS

Claims 1, 2, 6, 7, 27, and 31 to 36 are pending in the application. No claims have been amended, added, or canceled herein.

Applicants respectfully request reconsideration of the rejections of record in view of the following remarks.

Alleged Obviousness

Claims 1, 2, 6, 7, 27, and 31 to 36 have been rejected under 35 U.S.C. § 103(a) as allegedly obvious over U.S. Patent No. 5,804,184 ("the Filpula patent") in view of Takaku, H., *et al.*, *Jpn J Cancer Res* 86: 840-846 (1995) ("the Takaku reference"); Sugimura, K., *et al.*, *Melanoma Res* 2:191-196 (1992) ("the Sugimura reference"); and Oyanagi, K., *et al.*, *Tohoku J Exp Med* 148:385-91 (1986) ("the Oyanagi reference"). Applicants respectfully traverse the rejection because the Office Action has failed to establish *prima facie* obviousness.

The Office Action's assertion of obviousness is based upon an incorrect reading of the cited references, which, in fact, do not contain the teachings attributed to them by the Office Action. For example, the Sugimura reference reports that five human melanoma cell lines exhibited sensitivity to the growth inhibitory effects of arginine deiminase. The reference describes experiments in which the level of argininosuccinate synthetase in the five human melanoma cell lines was determined. (See page 193, second column to page 194, first column). The Office Action asserts that "the AD sensitivity of various tumor cells is attributed to the reduced level of ASS expression, as taught by Sugimura, et al." (Office Action dated December 22, 2003, page 3). The Sugimura reference, however, teaches only that arginine deiminase sensitivity of ***melanoma*** cells ***may*** be attributed to reduced levels of

argininosuccinate synthetase. Notably, the reference states that one melanoma cell line (G361) "exhibited a significant level of ASS gene expression...[but] was still highly sensitive to the growth inhibitory activity of AD." (See page 194, second column). The reference, therefore, does ***not*** teach that arginine deiminase sensitivity can be definitively attributed to reduced argininosuccinate synthetase expression in melanoma cells. Moreover, the reference contains no teachings whatsoever with respect to whether arginine deiminase sensitivity can be attributed to reduced levels of argininosuccinate synthetase in tumor cell types other than melanoma.

The Takaku reference describes experiments demonstrating that *Mycoplasma arginini* arginine deiminase (a-AD) inhibits the growth of mouse hepatoma cells and mouse fibrosarcoma cells *in vitro*. (See page 843, first column). The reference reports that the addition of L-arginine restored, in a dose-dependent manner, the growth inhibition caused by the a-AD. (See page 844, first column). The Office Action asserts that "[c]ancers such as carcinoma, melanoma or hepatoma that have been successfully treated by arginine deprivation (AD) therapy, all are deficient in or have reduced level of arginosuccinate synthetase, as taught by U.S. 5,804,184 [the Filpula patent], Takaku et al, and Oyanagi et al." (Office Action dated December 22, 2003, page 3). Contrary to the assertion made in the Office Action, however, the Takaku reference does not teach or suggest that the arginine deiminase-sensitive tumor cell lines tested (or any tumor cells lines for that matter) are deficient or have reduced levels of argininosuccinate synthetase. In fact, the reference states that "the mechanism by which [a-AD] causes inhibition of tumor cell growth is still unclear." (See page 840, second column).

Similarly, the Filpula patent and Oyanagi references also fail to teach or suggest that arginine deiminase sensitive tumor cells are deficient in, or have reduced levels of, argininosuccinate synthetase. For example, the Filpula patent describes arginine deiminase obtained from *Mycoplasma arthritides* and describes polymer conjugates of the *Mycoplasma arthritides* arginine deiminase. The patent states that the conjugates can be used to treat "carcinomas deficient in the enzyme arginosuccinate synthetase, e.g., melanoma (Sugimura, et al., 1992, Melanoma Res. 2: 191-196)." (See col. 13, lns. 15 to 19). The Filpula patent thus cites the Sugimura reference for the proposition that melanomas are deficient in argininosuccinate synthetase. As previously discussed, however, the Sugimura reference does not teach that arginine deiminase sensitivity can be definitively attributed to reduced argininosuccinate synthetase expression. Moreover, contrary to the assertion made in the Office Action, the Filpula patent fails to teach or suggest that tumor types other than melanomas are deficient in, or have reduced levels of, argininosuccinate synthetase.

Furthermore, the Oyanagi reference fails to teach or suggest that cancers such as carcinoma, melanoma, or hapatoma are deficient in, or have reduced levels of, argininosuccinate synthetase. The reference describes two case studies of patients suffering from citrullinemia and reports that reduced levels of argininosuccinate synthetase activity were detected in liver tissues of the patients, while normal argininosuccinate synthetase activities were detected in the patients' kidney and brain tissues. The reference fails to teach or suggest that any type of cancer cell, much less carcinoma, melanoma, or hapatoma, is deficient in, or has reduced levels of, argininosuccinate synthetase.

Notably, prior to Applicants' inventive efforts, it was not known whether a lack of argininosuccinate synthetase, argininosuccinate lyase, or citrulline transporter molecules was

responsible for imparting a requirement for arginine for the growth of cells that exhibit arginine deiminase sensitivity. Applicants were the first to demonstrate that tumor cells that are sensitive to arginine deiminase exhibit sensitivity because the cells lack argininosuccinate synthetase. The remaining possibilities, lack of argininosuccinate lyase or citrulline transporter molecules, were not excluded prior to Applicants' efforts.

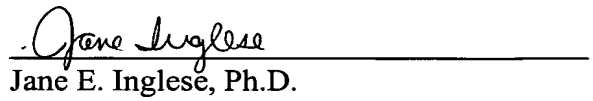
The Office Action has premised its finding of obviousness on an incorrect interpretation of the cited references and has, therefore, failed to properly establish *prima facie* obviousness. Moreover, as discussed in the Reply filed October 2, 2003, the Office Action has failed to establish that the cited references teach or suggest all the limitations of the claims. Notably, the Office Action concedes as much by stating that "the references do not directly teach methods for identifying cancer patients susceptible to arginine deprivation (AD) therapy." (Office Action dated December 22, 2003, page 3). In addition, the Office Action has failed to make of record any credible evidence that those of ordinary skill in the art would have been motivated to combine the teachings of the cited references. The Office Action merely offers the conclusory statement that "the idea of combining the above cited references clearly flows logically from their having been individually taught in the art." (Office Action dated December 22, 2003, page 4). Much more is required, however, to properly establish *prima facie* obviousness. *In re Lee*, 61 U.S.P.Q.2d 1430, 1433 (Fed. Cir. 2002) (stating that "[t]he factual inquiry whether to combine references must be thorough and searching. It must be based on ***objective evidence of record***. This precedent has been reinforced in myriad decisions, and cannot be dispensed with...***The need for specificity*** pervades this authority.")(emphasis added). Applicants accordingly, respectfully request withdrawal of the rejection.

Conclusion

Applicants believe that the foregoing constitutes a complete and full response to the Office Action of record. Accordingly, an early and favorable action is respectfully requested.

Respectfully submitted,

Date: March 16, 2004



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